Supplemental Material

Variation of radiation dose-response by chemotherapy treatment

Among non-radiation treated patients, there was a non-significant 2.4-fold RR of thyroid cancer for any chemotherapy treatment and 3 to 4.5-fold relative risk (RR) for specific treatments, alkylating agents, anthracyclines and bleomycin, and there were decreasing trends in RRs by chemotherapy treatment with increasing radiation dose, which were statistically significant for alkylating agents (p=0.02) and bleomycin (p=0.01) (Table 3). Using all data combined and adjusting for continuous radiation dose using model (3) allows for increased power to evaluate effect modification of chemotherapy RRs by radiation dose. We found significant effect modification by radiation dose for alkylating agents (p=0.03), anthracyclines (p=0.05) and bleomycin (p=0.02) (Table S1). In addition, for alkylating agents and anthracyclines, there was evidence that effect modification derived from a reduced strength of radiation association (i.e., different β's) for patients taking the agent, and not from differences in dose-response curvatures. Adjusting for radiation dose with model (3), the estimated RRs of thyroid cancer for non-radiation exposed patients for treatment by any chemotherapy, alkylating agents, anthracyclines or bleomycin were 2.2 (0.7-7.1), 4.0 (1.4-11.4), 3.4 (1.3-9.0) and 4.6 (1.6-12.9), respectively, which agreed closely with RRs in patients not treated with radiation (Table 3).

Table S1: Results for Testing Effect Modification of the Relative Risk (RR) for Radiation Dose by Chemotherapy for the Pooled Data.

		Any chemotherapy		Alkylating Agents		Anthracyclines		Bleomycin	
Model [a]	Prms [b]	Deviance [c]	P [d]	Deviance	P	Deviance	P	Deviance	P
$1 + \sum \beta_j z_j d \exp(\gamma_j z_j d)$	4	0.0	--	0.0	--	0.0	--	0.0	--
$1 + \beta d \sum z_j \exp(\gamma_j z_j d)$	3	0.1	0.72	3.1	0.08	4.4	0.04	0.2	0.63
$1 + \sum \beta_j z_j d \exp(\gamma d)$	3	0.4	0.52	0.8	0.38	0.0	0.99	2.2	0.13
$1 + \beta d \exp(\gamma d)$	2	0.5	0.48	7.1	0.03	6.2	0.05	7.5	0.02

[a] Linear-exponential (linear) model for radiation dose, d: $RR(d)=[1 + \sum \beta_j z_j d \exp(\gamma_j z_j d)]$ with β_j representing the linear slope parameter and γ_j the curvature, where z_j is an indicator variable for level j, j=1,2, denoting chemotherapy group (No/Yes).
[b] Number of parameters in the excess RR.
[c] Change in deviance relative to the full interaction model.
[d] P-value for the likelihood ratio test relative to the full interaction model.

Assessment of study-specific influence on the radiation relative risks

We fitted model (3) to all data combined and omitting one study in turn to evaluate the influence of any individual study on overall results. Figure S1 indicates that the fitted RRs at a dose of 10 Gy were not markedly influenced by any single study.

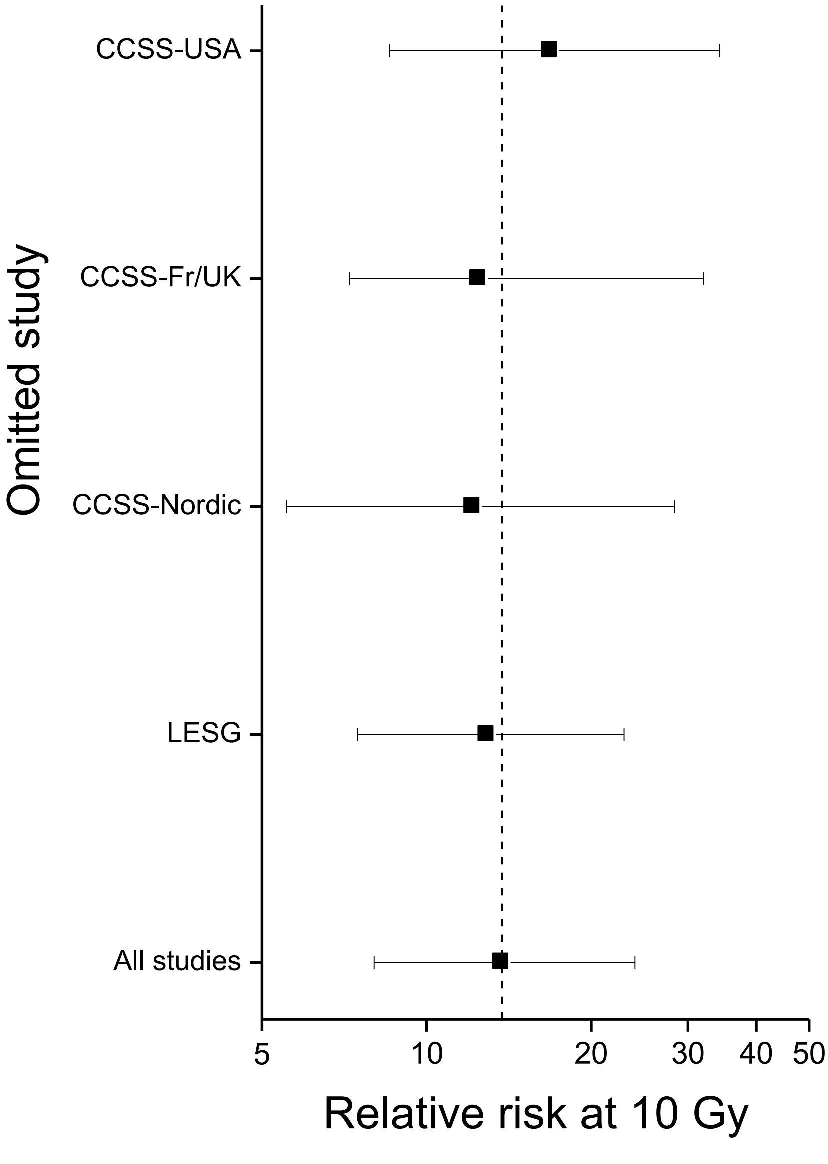

Figure S1: Fitted Relative Risk of Thyroid Cancer at 10 Gy Based on Model (3) for All Data Combined and for Data with One Study Omitted.

Table S2 indicated statistical homogeneity of the radiation effects across the four studies relative to the full interaction model (p=0.57). However, under a linear-exponential (linear-quadratic) model, there was evidence of heterogeneity (p=0.01), due entirely to the CCSS-US study, with the other three studies exhibiting homogeneity of radiation dose effects (p=0.53) (not shown).

Table S2: Results for Testing Effect Modifier of the Relative Risk (RR) for Radiation Dose Across the Four Studies.

Model [a]	Prms [b]	Deviance [c]	P [d]
$1 + \sum \beta_j\ z_j\ d \exp(\gamma_j\ z_j\ d)$	8	0.0	--
$1 + \beta\, d \sum z_j \exp(\gamma_j\ z_j\ d)$	5	3.3	0.35
$1 + \sum \beta_j z_j\ d \exp(\gamma\ d)$	5	1.1	0.77
$1 + \beta\ d\ \exp(\gamma\ d)$	2	4.8	0.57

[a] Linear-exponential (linear) model for radiation dose, d: $RR(d)=[1 + \sum \beta_j\ z_j\ d \exp(\gamma_j\ z_j\ d)]$ with β_j representing the linear slope parameter and γ_j the curvature, where z_j is an indicator variable for level j, j=1,…,4, denoting study.
[b] Number of parameters in the excess RR.
[c] Change in deviance relative to the full interaction model.
[d] P-value for the likelihood ratio test relative to the full model.

Dose response relationship under an excess absolute risk model

We fitted the excess absolute risk (EAR) model to the two cohort studies to evaluate the EAR(d) in radiation dose d using the same functional forms as for the ERR models. Table S3 indicates that a linear model did not fit the data for either study or for all data combined.

Table S3 - Parameter Estimates for the Best Fitting Excess Absolute Risk (EAR) Model [a] for Each of the Two Cohort Studies and For the Studies Combined.

Study	Model	$\beta \times 10^4$ (95% CI)	Curvature	P [b]	$EAR_{10\ Gy} \times 10^4$ (95%CI)
CCSS-Fr/UK	Linear-exponential (linear-quadratic)	2.85 (0.9-6.6)	γ_1: -0.1428 γ_2: 0.0018	0.03	8.15 (4.3-15.4)
CCSS-US	Linear-exponential (quadratic)	1.44 (1.0-2.1)	γ_2:-0.0013	<0.01	12.7 (8.9-18.1)
Pooled data [d]	Linear-exponential (quadratic)	1.29 (0.9-1.8)	γ_2:-0.0012	<0.01	12.4 (9.3-16.8)

[a] Models for radiation dose, d, include: linear-exponential (linear): EAR(d) = $\beta d \exp(\gamma_1 d)$; linear-exponential (quadratic): EAR(d) = $\beta d \exp(\gamma_2 d^2)$; and linear-exponential (linear-quadratic): EAR(d) = $\beta d \exp(\gamma_1 d + \gamma_2 d^2)$, where β defines the linear slope parameter in excess cases per person-year Gray (Gy) and γ_1 and/or γ_2 defines the curvature. Background risk adjusted for sex, attained age, chemotherapy, type of first cancer and year of birth.
[b] P-value for test of no departure from linearity, $\gamma_1 = 0$ and/or $\gamma_2 = 0$.
[c] Excess absolute risk at 10 Gy and 95% confidence interval (CI).
[d] Model further adjusted by study.

Our evaluation indicated that EAR models were heterogeneous for the two studies (p<0.01) (Table S4). Further analyses suggested that study heterogeneity derived from differences in both the EAR/PY-Gy and the curvature of the dose-response.

Table S4: Tests of Effect Modification of the Excess Absolute Risk (EAR) for Radiation Dose Across the Two Cohort Studies.

Model [a]	Prms [b]	Deviance [c]	P [d]
$\sum \beta_j\ z_j\ d \exp(\gamma_{1,j}\ z_j\ d + \gamma_{2,i}\ z_j\ d^2)$	12	0.0	--
$\beta\ d \sum z_j \exp(\gamma_{1,j}\ z_j\ d + \gamma_{2,j}\ z_j\ d^2)$	9	3.8	0.05
$\sum \beta_j\ z_j\ d \exp(\gamma_1\ d + \gamma_2\ d^2)$	6	14.0	<0.01
$\beta\ d \exp(\gamma_1\ d + \gamma_2\ d^2)$	3	14.1	<0.01

[a] Linear-exponential (linear-quadratic) model for radiation dose, d: EAR(d)= $\sum \beta_j\ z_j\ d \exp(\gamma_{1,j}\ z_j\ d + \gamma_{2,j}\ z_j\ d^2)$ with β_j representing the linear slope parameter and $\gamma_{1,j}$ and $\gamma_{2,j}$ the curvature parameters, where z_j is an indicator variable for level j, j=1,…,4, denoting study.
[b] Number of parameters in the excess EAR.
[c] Change in deviance relative to full interaction model.
[d] P-value for the likelihood ratio test relative to the full model.

The EAR modeling revealed that radiation dose had greater effects in females (p=0.01), younger ages at exposure, particularly under age 15 (p=0.03), and at increased time since radiation exposure (p<0.01) and attained age (p<0.01) (Table S5). The variations of the EAR/PY-Gy with calendar year and with attained age largely disappeared when we accounted for the variation of the EAR/PY-Gy with time since exposure (p=0.15 for calendar year and p=0.40 for attained age) (not shown). In contrast, variations of the EAR/PY-Gy with age at exposure and time since exposure remained statistically significant after adjustment for the other factor or for attained age.

Table S5: Estimates of Modification to the Linear Component (β) of the Excess Absolute Risk (EAR) Radiation Dose Model [a] for Each Cohort Study and For the Two Studies Combined.

Variable	CCSS-US		CCSS-Fr/UK		Pooled data		
	$\beta \times 10^4$	γ_2	$\beta \times 10^4$	γ_1/γ_2	$\beta \times 10^4$	γ_2	$EAR_{10\,Gy}$ [b] $\times 10^4$
Gender							
Male	0.99	-0.0013	2.95	-0.1439	0.91	-0.0012	8.9 (5.6-14.3)
Female	2.15		2.76	0.0018	1.90		18.8 (12.8-27.7)
P [c]	0.01		0.91		0.01		
Age at exposure (yrs)							
>5	1.25	-0.0011	4.03	-0.1419	1.30	-0.0009	12.9 (7.2-20.3)
5-9	1.52		2.04	0.0019	1.22		12.1 (7.2-20.3)
10-14	1.87		0.99 [d]		1.37		13.6 (7.9-23.5)
≥15	0.56				0.29		2.9 (0.6-13.7)
P [c]	0.08		0.24		0.03		
P-trend [e]	0.32		0.04		0.03		
Years since first exposure							
<15	0.74	-0.0013	0.69	-0.1404	0.56	-0.0012	5.6 (3.2-9.7)
15-19	2.74		7.25	0.0017	2.8		27.9 (18.3-42.6)
20-24	2.38		9.32		2.2		21.7 (11.8-39.9)
≥25	3.04		7.58		2.9		28.6 (15.2-54.0)
P [c]	<0.01		<0.01		<0.01		
P-trend [e]	<0.01		<0.01		<0.01		
Calendar year							
<1990	0.75	-0.0014	1.43	-0.0782	0.80	-0.0013	7.2 (4.4-11.9)
1990-1999	1.51		306	0.0007	1.36		11.8 (7.8-17.9)
≥2000	4.37		8.20		3.94		33.8 (22.0-51.9)
p [c]	<0.01		0.01		<0.01		
Attained age (yrs)							
<20	0.86	-0.0014	0.72	-0.0787	0.70	-0.0014	6.9 (3.9-12.0)
20-24	1.61		3.55	0.0007	1.69		16.7 (9.9-28.3)
25-29	1.92		4.79		1.94		19.1(10.9-33.4)
30-34	3.46		7.42		3.30		32.6 (19.1-55.6)
≥35	2.24		3.06		1.91		18.9 (8.0- 44.5)
P [c]	0.02				0.01		
P-trend [e]	0.01		0.01		<0.01		

[a] Models for radiation dose, d, include: linear-exponential (linear): $EAR(d) = \beta d \exp(\gamma_1 d)$ for CCSS-Fr/UK and pooled data; and linear-exponential (quadratic): $EAR(d) = \beta d \exp(\gamma_2 d^2)$ for CCSS-US, where β defines the slope parameter in excess cases per person-year Gy and γ_1 or γ_2 defining the curvature. For modifiers, βd was replace by ($\sum_j \beta_i z_j d$), where z_j was a zero/one indicator variable for the j^{th} category and β_i represented the linear component of the dose response relationship within the i^{th} category. Models adjusted for sex, attained age, chemotherapy, first cancer and year of birth, with additional adjustment by study for pooled data.

[b] Estimated EAR at 10 Gy.

[c] P-value for J-1 degrees of freedom likelihood ratio test of homogeneity of β_j across categories, i.e., $\beta_1 = \ldots = \beta_J$.

[d] Category merges all higher categories.

[e] P-value for linear trend using continuous variable.

Histology-specific results

We fitted model (3) to all thyroid cancer cases, to papillary tumors and to other tumor types (Tables S6a and S6b). Since papillary tumors included 82.4% (n=154) of all cases, results restricted to papillary tumors for the ERR and EAR modeling were similar to results for all data. Although there were only 33 thyroid cancers of other histologies, results for the ERR modeling and for the EAR modeling suggested these other histologies were also radiogenic ($p<0.01$).

Table S6a: Parameter Estimates for the Best Fitting Model [a] for the Excess Relative Risk (ERR) for All Thyroid Cancers, Papillary Tumors and Other Tumors Types.

Case group	β, (95% CI)	γ_1	P [b]	$RR_{10\,Gy}$ [c] (95% CI)
All thyroid cancers	2.38 (1.2-4.6)	-0.0628	<0.01	13.7 (8.0-24.0)
Papillary tumors	1.69 (0.8-3.6)	-0.0618	<0.01	10.1 (5.7-18.5)
Others	5.71 (0.9-36.3)	-0.0629	<0.01	31.4 (6.3-176.4)

[a] Models for radiation dose, d, used the linear-exponential (linear): $RR(d)=[1 + \beta\ d \exp(\gamma_1\ d)]$ with β defining the linear slope parameter and γ_1 defining the curvature. Models adjusted for sex, attained age, chemotherapy, first cancer , year of birth and study. The LESG study was excluded since there was no information on histology.
[b] P-value for test of no departure from linearity ($\gamma_1 = 0$).
[c] Estimated Relative Risk at 10 Gy

Table S6b - Parameter Estimates for the Best Fitting Excess Absolute Risk (EAR) Model [a] for the Two Cohort Studies Combined for All Thyroid Cancer, Papillary Tumors and Other Tumors Types.

Case group	$\beta\times10^4$ (95% CI)	γ_1	P [b]	$EAR_{10\,Gy}\times10^4$ (95% CI)
All thyroid cancers	1.84 (1.2-2.9)	-0.0547	<0.01	10.7 (7.8-14.6)
Papillary tumors	1.37 (0.8-3.4)	-0.0509	<0.01	8.2 (5.7-11.9)
Others	0.64 (0.0-1.3)	-0.0714	<0.01	3.1 (1.8-5.3)

[a] Models for radiation dose, d, used the linear-exponential (linear): $EAR(d) = \beta d \exp(\gamma_1\ d)$ and the linear-exponential (quadratic): $EAR(d) = \beta\ d \exp(\gamma_2 d^2)$, where β defines the linear slope parameter in excess cases per person-year Gy and γ_1 or γ_2 defines the curvature. Models adjusted for sex, attained age, chemotherapy, type of first cancer, year of birth and study.
[b] P-value for test of no departure from linearity ($\gamma_1 = 0$).
[c] Excess absolute risk at 10 Gy and 95% confidence interval (CI).